

# New Agents for Burkitt's Lymphoma May Reduce Immunosuppression

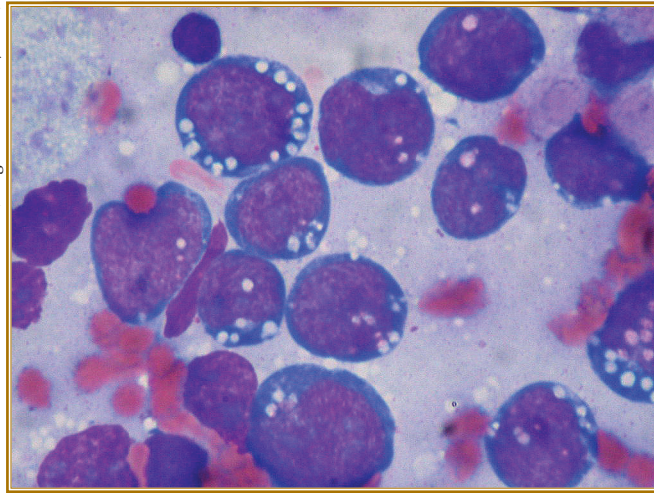
Rare in the United States, but more common in the developing world, Burkitt's lymphoma (BL) is an aggressive form of non-Hodgkin's lymphoma that typically responds well to treatment. The most successful treatments are highly immunosuppressive, however, so doctors usually prescribe them only for patients whom they can monitor and treat for infectious complications, such as the elderly and children in developing countries.

Now scientists have uncovered genetic signatures for BL that show, for the first time, that the illness is molecularly distinct from other lymphomas. Mutated genes and pathways within those signatures might be targets for new, less immunosuppressive therapies, reports Louis M. Staudt, M.D., Ph.D., Deputy Chief of CCR's Metabolism Branch, who led the study. These findings, published in *Nature* last October, may lead to effective, better tolerated treatment therapies for BL.

Staudt's research team showed previously that BL differs genetically from another non-Hodgkin's lymphoma known as diffuse large-B-cell lymphoma (DLBCL). BL has three recognized subtypes. These include a sporadic subtype diagnosed most often in children from developed countries, an Epstein-Barr virus-associated subtype that is endemic in Africa, and an HIV-associated subtype. Furthermore, the team was aware that c-myc—a tumor-promoting oncogene—is always active in this cancer, though the regulatory pathways that cooperate with c-myc were unknown.

Undaunted, the Staudt team set out to identify the specific genes and pathways in BL cells that enable

(Image: Ed Uthman, M.D.)



Burkitt's lymphoma cells

proliferation and survival. They screened biopsy samples from 28 patients with BL and 13 BL cell lines. They then compared the results to sequencing data from DLBCL biopsies and found a striking set of new mutations that were not present in DLBCL, nor in other types of cancer.

Among them, mutations affecting the transcription factor TCF3 and its negative regulator ID3 were observed most often, detected in up to 70 percent of the samples from sporadic cases and 40 percent of those from endemic cases.

Staudt's team found that when mutated, TCF3 and ID3 boost the expression of genes and proteins that drive cancer progression. One such protein is the B cell receptor, which detects foreign pathogens during an immune response, and promotes cancer cell survival by activating the PI(3) kinase pathway. The team also tested some of the new PI(3) kinase inhibitors in BL cell lines. "We found that they were toxic to every cell line that we had," Staudt reported. PI(3) kinase inhibitors are far less immunosuppressive than the chemotherapies currently used in BL treatment.

A different set of mutations was found to affect yet another gene controlled by TCF3, known as CCND3. This gene encodes for the protein cyclin D3, which regulates key phases of the cell cycle. But when mutated, cyclin D3 drives explosive rates of BL cell proliferation. "So driven by aberrations in the PI(3) kinase and cyclin D3 pathways, the BL cancer cell survives too long and it proliferates too much," Staudt said. Discovery of cyclin D3's involvement in BL may lead to new treatments.

NCI's recently established Center for Global Health plans to investigate these new therapeutic options for patients in the developing world. "But we are also looking for less toxic therapies for all BL patients," Staudt added.

To learn more about Dr. Staudt's research, please visit his CCR website at <http://ccr.cancer.gov/staff/staff.asp?name=staudt>.